UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,188	12/01/2003	Yoke Min Sin	2500-000017	9843

27572 7590 06/06/2005

HARNESS, DICKEY & PIERCE, P.L.C.
P.O. BOX 828
BLOOMFIELD HILLS, MI 48303

EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,188	SIN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *23-26 and 37-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,27-36 and 45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed March 17, 2005. Claims 1, 5, 11, 15, 20, 22, 27-36 and 46-47 have been amended. Claim 48 has been added. Claims 23-26 and 37-44 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The rejection of claims 1-6, 10-16, 20-22, 27-36 and 45-47, Wolf-Watz et al, Wang et al and further in view of Morinigo et al (pages 14-15, paragraph 14 of the previous Office action) should have only included claims 1-3, 5-6, 10-13, 15-16, 20-22, 27-36 and 45-47. The office apologizes for this typographical error.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Restriction Requirement

3. Applicant urges that they believe that Group I direct to a vaccine composition and Group II directed to a method of making a vaccine composition should be rejoined. Applicant refers to MPEP 806.05 (f) to support their position.

Applicant's arguments filed March 17, 2005 have been fully considered but they are not persuasive. To address Applicant's comments regarding rejoining the product and method of making. It is the Examiner's position that the two inventions are independent and distinct for the reasons stated in the Restriction requirement mailed

August 27, 2004 and in the Non-Final Office action mailed December 14, 2004. It should be noted that the restriction requirement was made final in the last Office action.

Rejections Withdrawn

4. In view of Applicant's amendment the following rejections are withdrawn.

a) objection to the specification, page 3, paragraph 2.

b) objection to claims 1-22, 27-36 and 45-47, page 3, paragraph 3.

c) objection to claims 1-22, 27-36 and 45-47, page 4, paragraph 4.

d) objection to claims 1-22, 27-36 and 45-47, page 4, paragraph 5.

e) objection to claims 1-22, 27-36 and 45-47, page 4, paragraph 6.

f) objection to claims 27-36, page 4, paragraph 7.

g) Rejection of claims 5 and 12 under 35 U. S.C. 112, second paragraph, page 9, paragraph 9 of the previous Office action.

h) Rejection of claim 20 under 35 U. S.C. 112, second paragraph, page 9, paragraph 10 of the previous Office action.

Rejections Maintained

5. The rejection under 35 U.S.C. 112, first paragraph (written description) is maintained for claims 1-22, 27-36, 45-47 and newly submitted claim 48 for the reasons set forth on pages 5-8, paragraph 8 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recombinant protein major adhesin protein of *Aeromonas hydrophila* (AHMA) does not reasonably provide enablement for derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila*. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification defines the term "polypeptide derivative" as any polypeptides in which one or more amino acids have been replaced by different amino acids and which retains the function or activity of the polypeptide (page 6). The specification fails to provide a structure for the, derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila.*

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein's structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polynucleotide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such protein.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984*", (page 315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book *"Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other proteins having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use proteins that are derivatives of the recombinant protein major adhesin protein of *Aeromonas hydrophila* in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the amino acid's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

Applicant urges that the specification is enabled for derivatives and variants based on co-pending application no. 10/220,986 that is incorporated by reference. Applicant urges that the application no. 10/220,986 teaches how to make and use variants of the recombinant adhesin protein of *Aeromonas hydrophila* with out undue experimentation. Applicant also teaches that the instant disclosure is sufficient to allow one skilled the art to make and use the claimed invention without undue

experimentation. Applicant urges that in light of the disclosure in the present application and application no. 10/220,986 the necessary experimentation is not unduly extensive, sufficient direction or guidance is provided by both disclosures, an adequate number of working examples are provided and the relative skill of those in the art is commonly recognized as quite high.

Applicant's arguments filed March 17, 2005 have been fully considered but they are not persuasive. The claims encompass any deletion or substitution including combinations thereof that are not defined. The instant specification has not taught which amino acids are deleted or substituted in the amino acid sequence to arrive at a derivative or fragment that is encompassed by the claimed invention. It should be remembered that the statute under 35 U.S.C. 112, first paragraph requires that Applicant teach how to make and use the claimed invention and not how to find fragments or derivatives of the recombinant adhesin protein of *Aeromonas hydrophila.* One of skill in the art would not conclude that Applicant has enabled the polypeptides used in the claimed vaccine since the structure of the claimed polypeptides has not been disclosed. Therefore, Applicant has not met the burden required under 35 U.S.C. 112, first paragraph. It should be noted that the enablement for the instantly claimed invention should not be based solely on the disclosure of a co-pending application (e.g. 10.220. 986). The instant specification does not provide enablement for the claimed invention. It should be remembered that each patent application is examined individually.

6. The rejection under 35 U.S.C. 102(a) is maintained for claims 1, 27-29 and 35-36 and newly submitted claim 48 for the reasons set forth on page 10, paragraph 11 of the previous Office Action.

The rejection was on the grounds that Irianto et al teach an oral vaccine composition comprising formalin-inactivated isolated from *Aeromomas hydrophila* and Freund's (see the Abstract and page 117). Irianto et al teach that the vaccine composition contained $2x10^7$ bacterial cells g^{-1} of the feed (page 117). The claim limitation "oral" is being viewed as a limitation of intended use. Claims limitations such as "wherein the proportion of water and oil in the emulsion further comprise 1:2, "wherein the proportion of water in the emulsion is equal" are being viewed as limitations of experimental design choice. Irianto et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Irianto et al teach oral administration of formalin-inactivated cells of *Aeromonas hydrophila*. Applicant urges that Irianto et al do not teach an oral composition comprising recombinant protein AHMA. Applicant urges that a prior art reference anticipated a claim only if it discloses each and every limitation found in the claim.

Applicant's arguments filed March 17, 2005 have been fully considered but they are not persuasive. Irianto et al teach a vaccine composition comprising *Aeromonas hydrophila*. Applicant asserts that the cell used in the invention of the prior art are dead cells. It should noted that there is no limitation in the claims under this rejection requiring that the components of the vaccine composition be live. To address Applicant's comments regarding Irianto et al do not teach a vaccine composition

comprising recombinant protein AHMA. It should be noted that the claimed vaccine compositions encompass proteins that are derivatives of recombinant AHMA. It should be noted that claim limitations such as "recombinant" and the method steps of preparing the claimed vaccine composition (in newly submitted claim 48) are process limitations in a product claim. It should be remembered that the products of the prior art reference appear to be the same as the product claimed by the applicant because they appear to possess the same or similar functional characteristics. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity relied upon. Applicant has provided no side-by-side comparison to show that the claimed vaccine composition differs from that of the prior art. Therefore, this prior art reference anticipates the claimed invention.

7. The rejection under 35 U.S.C. 102(b) is maintained for claims 1-3, 5-6, 10 and 27-29 and newly submitted claim 48 for the reasons set forth on page 11, paragraph 12 of the previous Office Action.

The rejection was on the grounds that Fang et al teach a vaccine composition comprising the 43 kDa major adhesin protein isolated from *Aeromonas hydrophila* and Freund's complete adjuvant (see the Abstract and page 139). Fang et al teach that the vaccine composition contained 150 $\mu g\ mL^{-1}$ of the protein (page 139). The claim limitation "oral" is being viewed as a limitation of intended use. Claims limitations such as "wherein the proportion of water and oil in the emulsion further comprise 1:2, "wherein the proportion of water in the emulsion is equal" are being viewed as limitations of experimental design choice. Fang et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Fang et al do not teach an oral composition comprising recombinant protein AHMA. Applicant urges that the route of delivering a vaccine is an important factor for successful immunization. Applicant urges that Fang et al do not address whether or not a vaccine composition containing proteins that exhibit immunogenicity when parenterally placed directly into tissue can be administered orally to fish so as to retain significant immunogenicity. Applicant urges that by choosing the powerful FCA as the adjuvant in their parenteral vaccine composition, Fang et al suggest that a powerful adjuvant may be required to achieve a significant immune response to AHMA proteins even when administered parenterally. Applicant urges that the recitation of the term "oral" is relevant to the understanding and context of the

invention. Applicant urges that Fang et al do not disclose recombinant protein AHMA, recombinant protein AHMA fragments or recombinant protein derivatives. Applicant urges that the protein in the prior art was isolated using potassium thiocyanate.

Applicant's arguments filed March 17, 2005 have been fully considered but they are not persuasive. Fang et al teach a vaccine composition comprising *Aeromonas hydrophila.* To address Applicant's comments regarding "routes of vaccine delivery", it should be noted that the claims are directed to a product, a vaccine and not a method of vaccine delivery. To address Applicant's comments regarding the use of an adjuvant, it is well known in the art to use adjuvants in vaccine compositions. To address Applicant's comments regarding the method used in the prior art to isolated the AHMA protein, it should be noted that the claims are directed to a vaccine and not a method of isolating a protein. It should be noted that the claim limitation "oral" is a limitation of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963).

It should noted that claim limitations such as "recombinant" and the method steps of preparing the claimed vaccine composition (in newly submitted claim 48) are process limitations in a product claim. It should be remembered that the products of the prior art reference appear to be the same as the product claimed by the applicant because they appear to possess the same or similar functional characteristics. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 29222-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon. Applicant has provided no side-by-side comparison to show that the claimed vaccine composition differs from that of the prior art. Therefore, this prior art reference anticipates the claimed invention.

8. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-3, 5-6, 10-13, 15-16, 20-21, 27-35, 45 and newly submitted claim 48 for the reasons set forth on pages 12-13, paragraph 13 of the previous Office Action.

The rejection was on the grounds that Wolf-Watz et al teach a fish vaccine comprising live avirulent invasive bacteria (see the Title and the Abstract). Wolf-Watz et al teach that the invasive bacteria strains may be produced from known fish pathogens including *Aeromonas hydrophila* (column 5). Wolf-Watz et al teach that the invention contemplates that the mutant strain of the invention may carry DNA sequences coding for an antigenic determinants from other fish pathogens and is capable of expressing the sequence (column 6). Wolf-Watz et al teach that the invention contemplates vaccines comprising bacteria the carry multiple determinants from different pathogenic fish and capable of expressing hybrid (fusion) determinants (column 7). Wolf-Watz et al teach that viruses such as infectious pancreatic necrosis virus and infectious hematopoietic necrosis virus may apart of the vaccine of the invention (column 6). Wolf-Watz et al teach that the bacteria of the invention contains $1x10^2$-$1x10^8$ bacteria/ml (column 8). Wolf-Watz et al teach that the vaccine of the invention can be added to fish feed (column 8).

Wolf-Watz et al do not teach the immobilization antigen repeat I of *Ichthyophythirius multifiliis* (FP).

Wang et al teach a vaccine composition comprising the immobilization antigen repeat I of *Ichthyophythirius* and Freund's incomplete adjuvant (see the Abstract). Wang et al teach that fish immunized with the FP antigen developed high titers of serum immobilized antibodies (see the Abstract). Wang et al teach that this study shows there is a clear role for the immobilization antigen repeat I of *Ichthyophythirius* in protection (see the Abstract). The claim limitation "recombinant" is being viewed as a process limitation.

It would be *prima facie* obvious at the time the invention was made to add the immobilization antigen repeat I of *Ichthyophythirius* as taught by Wang et al to the vaccine composition of Wolf-Watz et al because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising proteins from *Aeromonas hydrophila* and immobilization antigen repeat I of *Ichthyophythirius* would be effective in protecting against a broad spectrum of fish diseases.

Applicant urges that Wolf-Watz et al discuss the advantages of live vaccines over vaccines that are comprise killed pathogens or bacterial components. Applicant urges

that Wolf-Watz et al teach away from the present claims which teach an oral vaccine composition based on bacterial component proteins optionally in combination with killed pathogens. Applicant urges that a *prima facie* case of obvious has not been established because the primary reference teaches away from the claimed invention.

In response to applicant's argument regarding establishment of a *prima facie* case of obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, Wolf-Watz et al teach vaccines comprising *Aeromonas hydrophila.* Wolf-Watz et al do not teach other antigens such as *Ichthyophythirius.* Wang et al teach vaccines comprising *Ichthyophythirius.* One of ordinary skill in the art would be motivated to combine the teachings of the prior art references because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens. Therefore, a case of *prima facie* obviousness has been established. The Examiner disagrees with Applicant's assertion that the prior art teaches away from the claimed invention. It should be noted that the prior art teaches oral administration of vaccine compositions because Wolf-Watz et al teach that the vaccines of the invention can be added to fish feed (see column 8). It should be noted that claim limitations such

as the method steps of preparing the claimed vaccine composition (in newly submitted claim 48) are process limitations in a product claim. There is nothing on the record to suggest that the combination of references do not teach the claimed invention.

9. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-3, 5-6, 10-13, 15-16, 20-22, 27-36, 45-47 and newly submitted claim 48 for the reasons set forth on pages 14-15, paragraph 14 of the previous Office Action.

The rejection was on the grounds that Wolf-Watz et al and Wang et al as combined above do not teach *Vibrio alginolyticus.*

Morinigo et al teach that a divalent vaccine composition comprising *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida*. Morinigo et al teach that the concentration of protein 800 mg ml^{-1} (page 299).Morinigo et al teach that high protection was conferred by the divalent vaccine (page (302).

It would be *prima facie* obvious at the time the invention was made to add the *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens as taught by Morinigo et al to the vaccine composition of Wolf-Watz et al and Wang et al as combined above because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens (column 7). It would be expected barring evidence to the contrary that a vaccine comprising proteins from *Aeromonas hydrophila,* immobilization antigen repeat I of *Ichthyophythirius,* and *Vibrio alginolyticus* and *Photobacterium damselae subsp. Piscicida* antigens would be effective in protecting against a broad spectrum of fish diseases.

Applicant urges that Wolf-Watz et al teach away from the present claims which teach an oral vaccine composition based on bacterial component proteins optionally in combination with killed pathogens. Applicant urges that a *prima facie* case of obvious has not been established because the primary reference teaches away from the claimed invention.

In response to applicant's argument regarding establishment of a *prima facie* case of obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, Wolf-Watz et al teach vaccines comprising *Aeromonas hydrophila.* Wolf-Watz et al do not teach other antigens such as *Ichthyophythirius.* Wang et al teach vaccines comprising *Ichthyophythirius.* Wolf-Watz et al and Wang et al as combined above do not teach *Vibro alginolyticus* or *Photobacterium damselae subsp. Piscicida.* Morinigo et al teach vaccine compositions comprising *Vibro alginolyticus* or *Photobacterium damselae subsp. Piscicida* . One of ordinary skill in the art would be motivated to combine the teachings of the prior art references because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens. Therefore, a case of *prima facie* obviousness has been established.

The Examiner disagrees with Applicant's assertion that the prior art teaches away from the claimed invention. It should be noted that the prior art teaches oral administration of vaccine compositions because Wolf-Watz et al teach that the vaccines of the invention can be added to fish feed (see column 8). It should be noted that claim limitations such as the method steps of preparing the claimed vaccine composition (in

newly submitted claim 48) are process limitations in a product claim. There is nothing on the record to suggest that the combination of references do not teach the claimed invention.

10. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-6, 10-16, 20-22, 27-36, 45-47 and newly submitted claim 48 for the reasons set forth on pages 14-15, paragraph 14 of the previous Office Action.

The rejection was on the grounds that Wolf-Watz et al, Wang et al and Morinigo et al as combined above do not teach palm oil.

Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). Chen et al teach that the compositions of the invention that contain organic oils such as palm oil are stable compositions (column 5).

It would be *prima facie* obvious at the time the invention was made to add the palm oil as taught by Chen et al to the vaccine composition of Wolf-Watz et al, Wang et al and Morinigo et al as combined above because Chen et al teach the that organic oil such as palm oil can be used to provide improved delivery of polyfunctional active ingredients (columns 5 and 6). It would be expected barring evidence to the contrary that a vaccine comprising palm oil would be effective stabilizing vaccines at improving delivery of polyfunctional active ingredients.

Applicant urges that Chen et al disclose that the oil component of the oil-in-water emulsion may not be appropriately polar to effectively incorporate polyfunctional active ingredients at desirable therapeutic levels without compromising product safety. Applicant urges that a *prima facie* case of obvious has not been established.

In response to applicant's argument regarding establishment of a *prima facie* case of obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so

found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case , the combination of references do not teach palm oil. One of ordinary skill in the art would be motivated to combine the teachings of the prior art references because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad spectrum protection against a range of fish pathogens and one of ordinary skill in the art would be motivated to add palm oil to the vaccine compositions. One would be motivated to add palm oil to the vaccine composition as combined above because Chen et al teach that compositions comprising palm oil are stable compositions. Additionally, Chen et al teach that palm oil improves delivery of active ingredients. Therefore, a case of *prima facie* obviousness has been established.

The Examiner disagrees with Applicant's assertion that the prior art teaches away from the claimed invention. It should be noted that the prior art teaches oral administration of vaccine compositions because Wolf-Watz et al teach that the vaccines of the invention can be added to fish feed (see column 8). It should be noted that claim limitations such as the method steps of preparing the claimed vaccine composition (in newly submitted claim 48) are process limitations in a product claim. There is nothing on the record to suggest that the combination of references do not teach the claimed invention.

11. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-22, 27-36, 45-47 and newly submitted claim 48 for the reasons set forth on pages 16-17, paragraph 16 of the previous Office Action.

The rejection was on the grounds that Calanchi et al teach that binding agents such as carboxymethylcellulose
(column 3). Calanchi et al teach that binders are soluble in water and solvents (column 3). Calanchi et al teach that binders are often used to thicken the composition (column 4).

It would be *prima facie* obvious at the time the invention was made to add carboxymethylcellulose as taught by Calanchi et al to the vaccine composition of Wolf-Watz et al, Wang et al, Morinigo et al and Chen et al as combined above because Calanchi et al teach that binders are often used to thicken the composition and have the property of dispersing and dissolving quickly in water or aqueous vehicles (see the Abstract). It would be expected barring evidence to the contrary that a vaccine comprising binding agents such as carboxymethylcellulose would be effective at making the components of the composition easily to disperse and dissolve quickly in water or aqueous vehicles.

Applicant urges that Applicant urges that a *prima facie* case of obvious has not been established. Applicant urges that the primary reference teaches away from the claimed invention. Applicant urges that Calanchi et al methods of dispersing thickening agents in pharmaceutical formulations.

In response to applicant's argument regarding establishment of a *prima facie* case of obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir.

1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant the reference as combined above do not teach carboxymethylcellulose. One of ordinary skill in the art would be motivated to combine the teachings of the prior art references because Wolf-Watz et al teach that the vaccine of the invention may comprise one or more antigens that are pathogenic to fish to produce a vaccine that provides broad-spectrum protection against a range of fish pathogens. One of skill in the art would add carboxymethylcellulose to the vaccine composition because Calanchi et al teach that thickener such as carboxymethylcellulose may be added to pharmaceutical formulations. Therefore, a case of *prima facie* obviousness has been established.

The Examiner disagrees with Applicant's assertion that the prior art teaches away from the claimed invention. It should be noted that the prior art teaches oral administration of vaccine compositions because Wolf-Watz et al teach that the vaccines of the invention can be added to fish feed (see column 8). It should be noted that claim limitations such as the method steps of preparing the claimed vaccine composition (in newly submitted claim 48) are process limitations in a product claim. There is nothing on the record to suggest that the combination of references do not teach the claimed invention.

Status of Claims

12. No claims allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

14. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
June 1, 2005

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600